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Review

# Calcium channels and migraine ☆

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ABSTRACT

Missense mutations in CACNA1A, the gene that encodes the pore-forming $\alpha_1$ subunit of human voltage-gated $Ca_V2.1$ (P/Q-type) calcium channels, cause a rare form of migraine with aura (familial hemiplegic migraine type 1: FHM1). Migraine is a common disabling brain disorder whose key manifestations are recurrent attacks of unilateral headache that may be preceded by transient neurological aura symptoms. This review, first, briefly summarizes current understanding of the pathophysiological mechanisms that are believed to underlie migraine headache, migraine aura and the onset of a migraine attack, and briefly describes the localization and function of neuronal $Ca_V2.1$ channels in the brain regions that have been implicated in migraine pathogenesis. Then, the review describes and discusses i) the functional consequences of FHM1 mutations on the biophysical properties of recombinant human $Ca_V2.1$ channels and native $Ca_V2.1$ channels in neurons of knockin mouse models carrying the mild R192Q or severe S218L mutations in the orthologous gene, and ii) the functional consequences of these mutations on neurophysiological processes in the cerebral cortex and trigeminovascular system thought to be involved in the pathophysiology of migraine, and the insights into migraine mechanisms obtained from the functional analysis of these processes in FHM1 knockin mice. This article is part of a Special Issue entitled: Calcium channels.

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**Contents**



## 1. Introduction

Migraine is a remarkably common episodic neurological disorder (e.g. it affects 17% of females and 8% of males in the European population [1]) characterized by recurrent attacks of typically throbbing and unilateral, often severe, headache with certain associated features such as

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nausea, phonophobia and/or photophobia; in a third of patients the headache is preceded by transient neurological symptoms, that are most frequently visual, but may involve other senses (migraine with aura: MA) [2]. Migraine is a complex genetic disorder, with heritability estimates as high as 50% and a likely polygenic multifactorial inheritance [3]. Although recent genome-wide association studies have identified a few risk factors for migraine [4–6], most of our current molecular understanding comes from studies of familial hemiplegic migraine (FHM), a rare monogenic autosomal dominant form of MA [3,7,8].

Three FHM causative genes have been identified, all encoding ion channels or transporters [9–11]. FHM type 1 (FHM1) is caused by missense mutations in CACNA1A (chromosome 19p13), that encodes the pore-forming $\alpha_1$ subunit of human voltage-gated $Ca_V2.1$ (P/Q-type) calcium channels [9].

$Ca_V2.1$ channels are located in presynaptic terminals and somatodendritic membranes throughout the mammalian brain and spinal cord [12], and play a prominent role in initiating action potential (AP)-evoked neurotransmitter release at central nervous system synapses [13]. At many central synapses P/Q-, N- and R-type $Ca^{2+}$ (Ca) channels cooperate in controlling neurotransmitter release, but P/Q-type channels have a dominant role, partly because of a more efficient coupling to the exocytotic machinery [14–16]. Moreover, at many central synapses, there is a developmental change in the Ca channel types mediating synaptic transmission, whereby the relative contribution of P/Q-type channels to release increases with postnatal age, until release becomes exclusively dependent on P/Q-type channels [17]. Among the presynaptic Ca channels, $Ca_V2.1$ channels are unique also in their capacity for interacting with and being modulated in a complex manner by a number of Ca-binding proteins ([18] for review and references). As a result, $Ca_V2.1$ channels may exhibit both Ca-dependent inactivation and Ca-dependent facilitation. Ca-dependent regulation of presynaptic $Ca_V2.1$ channels may play a crucial role in short-term synaptic plasticity during trains of action potentials [19–21]. Differential expression of the different Ca-dependent regulatory proteins and/or of different $Ca_V2.1$ splice variants may provide a means of neuron-type specific regulation of presynaptic P/Q channels and short-term plasticity. The somatodendritic localization of $Ca_V2.1$ channels points to additional postsynaptic roles, e.g. in neural excitability [22,23], gene expression [24] and cell survival [25].

The FHM1 mutations produce substitutions of conserved aminoacids in important functional regions of the $Ca_V2.1$ channel including the pore lining and the voltage sensors (see [8,26] for recent reviews and references). A few additional CACNA1A missense mutations affecting conserved aminoacids have been found in patients with sporadic hemiplegic migraine (SHM1) with similar symptoms as FHM but whose parents did not carry the mutation (e.g. [27]). Fig. 1 shows the location of FHM1 (and a few SHM1) mutations in the secondary structure of the $Ca_V2.1\alpha_1$ subunit, consisting of four repeated domains (I–IV) each of which contains six transmembrane segments (S1–S6) and a pore loop connecting S5 and S6 [28].

FHM1 can be considered a model for the common forms of migraine because, apart from the motor weakness or hemiparesis during aura (and the possibly longer aura duration), *typical* FHM attacks resemble MA attacks [2] and both types of attacks may alternate in patients and co-occur within families [3,7,8]. However, several FHM1 families show permanent cerebellar symptoms (such as slowly progressive cerebellar ataxia and/or nystagmus with cerebellar atrophy in some cases), that are usually not observed in common migraines. Pure FHM1 and FHM1 with cerebellar symptoms are usually associated with different mutations. Moreover, in addition to typical attacks, patients of some FHM1 families can have atypical severe attacks with signs of diffuse encephalopathy, impairment of consciousness (coma) or confusion, fever, prolonged hemiplegia lasting several days, and in a few cases seizures; this severe clinical phenotype is shown by most SHM1 patients. [8,29]. The incomplete penetrance of FHM1 (67% in a population-based sample of FHM families: [30]) and the symptom variability among subjects with the same mutation suggests that other genetic or environmental factors also influence the phenotype [8,29].

Two different FHM1 knockin mouse models have been generated by introducing the human R192Q and S218L mutations into the orthologous *cacna1a* $Ca_V2.1$ channel gene [31,32]. Whereas mutation R192Q causes in humans pure FHM, mutation S218L causes a particularly dramatic clinical syndrome, that may consist of, in addition to attacks of hemiplegic migraine, slowly progressive cerebellar ataxia and atrophy, epileptic seizures, coma or profound stupor and severe, sometimes fatal, cerebral edema which can be triggered by only a trivial head trauma [32,33]. Whereas homozygous R192Q and heterozygous S218L knockin mice did not exhibit an overt phenotype, homozygous S218L mice exhibited mild permanent cerebellar ataxia, spontaneous attacks of hemiparesis and/or (sometimes fatal) generalized seizures, and brain edema after only a mild head impact, thus modeling the main features of the severe S218L clinical syndrome [31,32].

Here, I first briefly summarize current knowledge of the main pathophysiological mechanisms that are believed to underlie migraine and describe the localization and function of neuronal $Ca_V2.1$ channels in the brain regions that have been implicated in migraine pathogenesis. Then, I review current knowledge of i) the functional consequences of

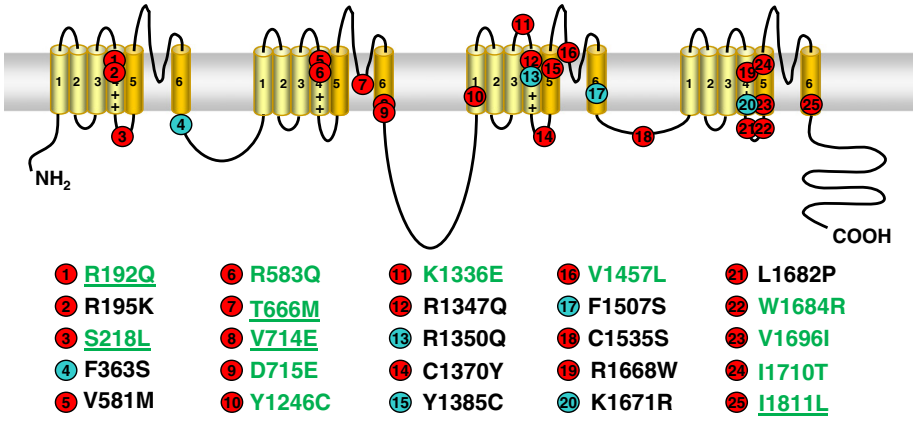


**Fig. 1.** Location of FHM1 (red) and SHM1 (blue) mutations in the secondary structure of the $Ca_V2.1\alpha_1$ subunit. Given the difficulty in distinguishing a pathogenic mutation from a rare polymorphic variant in the sporadic cases, only SHM1 mutations not found in either controls or parents and affecting conserved aminoacids are shown. Also not shown are: the SHM1 mutation V1696F (in the same location as the FHM1 mutation V1696I) found in a monozygotic twin pair with complex symptoms that clinically overlaps with both alternating hemiplegia of childhood and FHM [143], and two other probable FHM1 mutations found in individuals with a strong family history although other family members were not genotyped: P225H in the S3–S4 loop of domain I [144] and V581L in the same location as V581M [145]. Reference sequence Genbank Acc. No. X99897. The mutations written in green are those whose effects on the biophysical properties of recombinant $Ca_V2.1$ channels have been studied in heterologous expression systems; the mutations underlined are those whose effects have been studied also in transfected neurons from $Ca_V2.1^{-/-}$ mice expressing human $Ca_V2.1\alpha_1$ subunits.

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